

Weak ELF Magnetic Field Effects on Hippocampal Rhythmic Slow Activity

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Several investigations have revealed that electrical activity within the central nervous system (CNS) can be affected by exposure to weak extremely-low-frequency (ELF) magnetic fields. Many of these studies have implicated CNS structures exhibiting endogenous oscillation and synchrony as optimal sites for field coupling. A particularly well characterized structure in this regard is the rat hippocampus. Under urethane anesthesia, synchronous bursting among hippocampal pyramidal neurons produces a large-amplitude quasi-sinusoidal field potential oscillation, termed “rhythmic slow activity” (RSA) or “theta.” Using this *in vivo* model, we investigated the effect of exposure to an externally applied sinusoidal magnetic field (16.0 Hz; 28.9 μT_{rms}) on RSA. During a 60-min exposure interval, the probability of RSA decaying to a less coherent mode of oscillation, termed “large irregular-amplitude activity” (LIA), was increased significantly. Moreover, this instability persisted for up to 90 min postexposure. These results are consistent with the hypothesis that endogenous CNS oscillators are uniquely susceptible to field-mediated perturbation and suggest that the sensitivity of these networks to such fields may be far greater than had previously been assumed. This sensitivity may reflect nonlinearities inherent to these networks which permit amplification of endogenous fields mediating the initiation and propagation of neuronal synchrony. © 1998 Academic Press

Key Words: hippocampus; theta; rhythmic slow activity; magnetic field; extremely-low-frequency; oscillation; synchrony.

INTRODUCTION

A growing body of evidence suggests that weak extremely low frequency (ELF; 1–100 Hz) electric and magnetic fields may affect central nervous system (CNS) function. Exposure to exogenous ELF fields has been associated with effects involving reaction time (17, 20), learning and memory (18, 37), $^{45}\text{Ca}^{2+}$ efflux from brain slices (3, 9), and neuronal field potentials measured both *in vivo* (7, 8) and *in vitro* (5, 6). Endogenous ELF fields on the other hand have been implicated

primarily in the initiation and propagation of oscillation and synchrony within cerebral structures (26, 35). The mechanism(s) whereby these fields exert their influence, and the manner in which they interact with other processes within the CNS, has yet to be determined.

Involvement of endogenous fields in CNS oscillation and synchrony was first demonstrated by Libet and Gerard (26), who reported that insertion of a nonconducting barrier between otherwise isolated portions of frog olfactory bulb prevented the propagation of oscillatory potentials between them. More recently, endogenous fields have been shown to participate in the emergence of highly synchronous neuronal discharges in hippocampal slices maintained in Ca^{2+} -depleted media, in which synaptic transmission is blocked (21, 35). In this context, endogenous fields appear to exert their influence by synchronizing subthreshold membrane potential oscillations (MPOs) among hippocampal pyramidal neurons, thereby increasing the probability of coincident action potential generation within the ensemble (21, 36).

Endogenous field effects have also been implicated in another mode of hippocampal oscillation, referred to as “rhythmic slow activity” (RSA) (12, 25). The most widely investigated RSA variant (Type 2) is associated with muscarinic cholinergic receptor activation and is unaffected by most anesthetics (34). This form of RSA has been extensively investigated *in vivo* using urethane-anesthetized rats (12), and *in vitro* using rat hippocampal slices perfused with artificial cerebral spinal fluid containing the acetylcholine agonist carbachol (11, 28). In both preparations, RSA is variably interrupted by intervals of less coherent oscillation referred to as “large irregular-amplitude activity” (LIA) (12, 32) (Fig. 1).

The medial septal nucleus and nucleus of the diagonal band have been suggested to function as pacemakers in generating RSA, via cholinergic projections from these nuclei to the hippocampus (34). However, the emergence of RSA in the carbachol hippocampal slice preparation, which lacks these septal inputs, suggests that intrahippocampal possesses contribute substan-

tially to the generation of RSA. MPOs analogous to those associated with burst activity in the Ca^{2+} -depleted hippocampal slice model have been observed to be phase coupled to RSA both *in vivo* (33) and *in vitro* (25). This suggests further that endogenous field effects may be among the intrahippocampal mechanisms which mediate RSA. The hippocampus provides a particularly favorable environment for such field interactions in that the parallel alignment of pyramidal neurons, the unusually close packing of pyramidal cell bodies, and the relative absence of intervening neuroglia act to promote intracellular rather than extracellular current flow (16).

To the extent that endogenous field interactions contribute to hippocampal oscillation and synchrony, exogenously applied fields may be capable of modulating or disrupting this rhythmicity via perturbation of these interactions. Indeed, it has recently been shown that synchronous bursting associated with epileptiform activity in hippocampal slices can be suppressed by appropriately oriented application of weak static electric fields (19). Application of weak ELF magnetic fields has also been recently shown to disrupt RSA *in vitro* (4). It remains to be determined, however, whether analogous effects will occur *in vivo*, with parahippocampal network associations intact.

We investigated the effect of exposure to a weak sinusoidal ELF magnetic field on *in vivo* RSA using urethane-anesthetized rats. To ease interpretation of the results, the exposures were carried out in an environment in which static magnetic fields were eliminated. This limits the means of transduction to either Faraday induction or direct AC magnetic coupling and precludes the involvement of coupling mechanisms requiring combined static and alternating magnetic fields (10, 24, 27).

METHODS

Male Sprague-Dawley rats (300–500 g), housed under standard conditions, were anesthetized via a series of intraperitoneal injections of urethane in aqueous solution (0.5 g/ml), such that a total dosage of approximately 1.5 g/kg was approached asymptotically over a period of 1 h. Once anesthetized, the femoral vein was cannulated to permit subsequent intravenous injections of urethane. Rats were then placed on a temperature-regulated platform, maintained at 37°C, and mounted in a stereotactic instrument. The dorsal surface of the cranium was exposed to permit removal of a 3×2 -mm section of the cranial plate and underlying dura over the right cerebral hemisphere. Within this region, the (1 μm) tip of a lacquer-insulated tungsten microelectrode (1 M Ω) was stereotactically positioned 3.4 mm caudal to bregma, 2.4 mm lateral to the midline, and 2.8 mm ventral to the cortical surface.

This position was histologically confirmed to be centered within the stratum radiatum of the CA1 hippocampus (31). A stainless-steel reference electrode was inserted into the left frontal cortex through a burr-hole, positioned approximately 3 mm rostral to bregma and 2 mm lateral to the midline.

Signal from the two electrodes was differentially amplified and filtered to pass between 1 and 100 Hz (Grass, Model P600). The amplifier output was divided: one channel was fed to a real-time power spectrum analyzer (Bruel & Kjaer, Model 2031), digitally sampled at 128 Hz; the other channel was fed to an analog-to-digital converter (Axon Instruments, Model TL-2), digitally sampled at 300 Hz, and stored to disk for processing off-line (Fig. 2). Both the frame and the rat were attached through separate connections to a common earth ground.

Real time power spectra were sampled at 10-min intervals throughout the experiment, so that the power spectral distribution could be monitored. Data analysis was performed off-line using sets of 32768 data points sampled at 5-min intervals from the stored data. Each sample represented approximately 110 s of time-series data, beginning at $t = 0$ and continuing throughout the experiment (Axotape 2.1 and Matlab 4.0). Power spectral averages were generated for each set by sequentially averaging eight, 4096-point power spectra, with a full-scale frequency of 150 Hz and a frequency resolution of 0.0732 Hz.

The stereotax was positioned such that the rat's head was centered within a Helmholtz coil array. The rat's symmetry axis was aligned with that of a horizontally oriented coil, and parallel to the horizontal axis of the local geomagnetic field. This coil had two independent sets of windings which were energized separately to produce two magnetic fields: a DC field, which nulled the horizontal component of the local geomagnetic field ($\sim 18.4 \mu\text{T}$); and a $28.9 \mu\text{T}_{\text{rms}}$, 16.0 Hz sinusoidal field. The other coil in the array was oriented vertically and was energized to produce a DC magnetic field which nulled the vertical component of the local geomagnetic field ($\sim 53.2 \mu\text{T}$). The combined static fields created a "zero DC field" ($0.00 \pm 0.01 \mu\text{T}$) environment, upon which the AC magnetic field was superimposed during exposure.

Magnetic fields were calibrated using a fluxgate magnetometer prior to initiating the surgery. The magnetometer probe was positioned using a device which mounted within the stereotactic frame such that the active domain of the probe was within the region normally occupied by the rat brain, with the stereotactic instrument configured as it was during recording. The device had three intersecting, orthogonally aligned cylinders which, when mounted, oriented the probe along the geomagnetic N-S, E-W, and vertical axes. During the experiment, the fields were monitored with

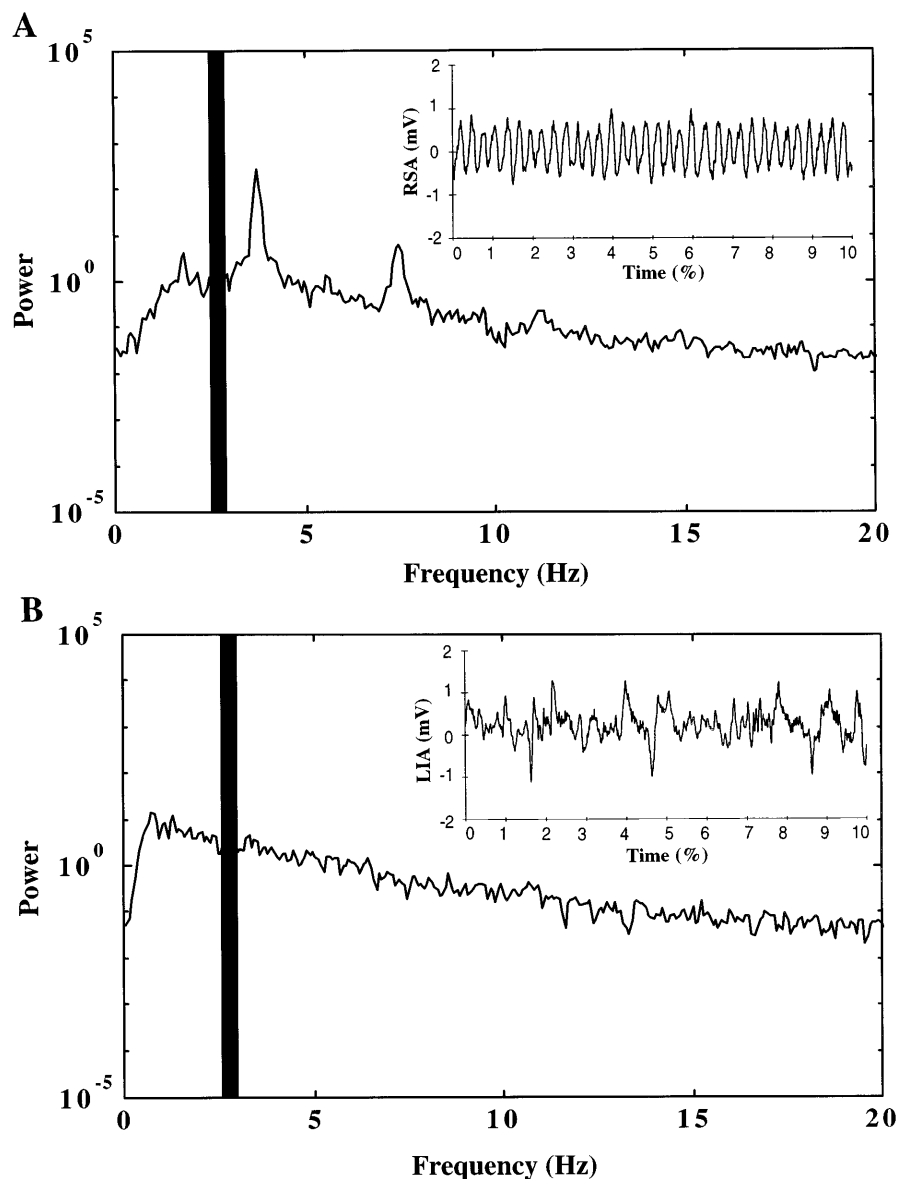


FIG. 1. Sample waveforms and power spectra obtained from rat CA1 hippocampus. (A) Rhythmic slow activity (RSA) power spectra. (A, inset) Representative RSA time-series. (B) Large irregular-amplitude activity (LIA) power spectra. (B, inset) Representative LIA time-series. Vertical bar pictured in both power spectra at 2.5 Hz represents the frequency cutoff used to operationally define RSA and LIA.

the probe positioned remotely within the exposure environment.

Animals were assigned randomly to either the experimental or control group. Once an animal was mounted and prepared for recording, a minimum of 15 min was allowed for acclimation prior to beginning data collection. Each experiment utilized the sequence: 60 min preexposure, 60 min exposure, 90 min postexposure. RSA stability during the preexposure period, defined as near absence of LIA (accepting no more than 10 LIA transients, each less than 15 s duration), was additionally required for inclusion as a member of either group. All animals resided in the “zero DC field” environment

continuously during the preexposure, exposure and postexposure intervals. However, only experimental group animals had the AC field applied during the exposure interval.

RESULTS

Analysis of preliminary data resulted in the selection of the dominant power spectral frequency as our dependent variable because of its relative stability within both the RSA and LIA states. These states were operationally defined as having dominant power spectral frequencies above and below 2.5 Hz, respectively (Fig. 1).

Transitions between RSA and LIA states were abrupt, thus the distribution of our dependent variable was non-Gaussian (bimodal). We therefore selected the method of generalized estimating equations (GEE) for our statistical analysis. The GEE method requires only that the relationship between the means associated with the RSA and LIA states, together with their respective variance and covariance, be specified. Generalized estimating equations, generated from correlation matrices, give consistent estimators of the regression coefficients and of their variances, under weak assumptions about the correlation among a subjects observations (38).

Of a total of 20 experimental trials, 8 rats were successfully assigned to the experimental group and 7 were assigned to the control group. The results of these experiments indicated that, relative to controls, experimental animals were significantly more likely to undergo a theta decay to LIA during both the exposure ($P < 0.05$) and postexposure intervals ($P < 0.02$). Combining both intervals produced a significance level of $P < 0.005$. Exposure to the AC magnetic field increased the probability of theta decay by a factor of 10 during exposure and by a factor of 6 during postexposure. These results are plotted as an RSA-decay event histogram in Fig. 3.

DISCUSSION

The results presented in this report are generally consistent with those obtained in analogous investiga-

tions using an *in vitro* RSA model (4). Both sets of results are remarkable because of the extremely weak field intensities employed.

We hypothesize that the disruption of hippocampal RSA is mediated by Faraday-induced currents. The degree to which alternating magnetic fields are able to induce these currents within a cerebral structure is determined by the regional, and generally anisotropic, conductive properties of the involved tissue (30). There are also physical constraints which determine whether such currents will exert an influence on neuronal excitability. In this context four characteristics have been identified: (1) extracellular resistivity (R_e)—a high R_e relative to intracellular resistivity (R_i) enhances current flow within neurons relative to the extracellular space; (2) cellular orientation—parallel arrays of neurons provide circuitual conduction pathways when current sources and sinks are spatially segregated within individual cells; (3) neuronal activation/synchrony—promotes summation of field-induced currents and positive feedback interactions; and (4) passive membrane properties—large diameter neurons with relatively low membrane capacitance promote the intracellular channeling of resistive currents (16). These same characteristics also determine the extent to which currents generated by endogenous fields are capable of influencing neuronal excitability.

The anatomy and physiology of the hippocampus are such that all of these conditions are satisfied (36).

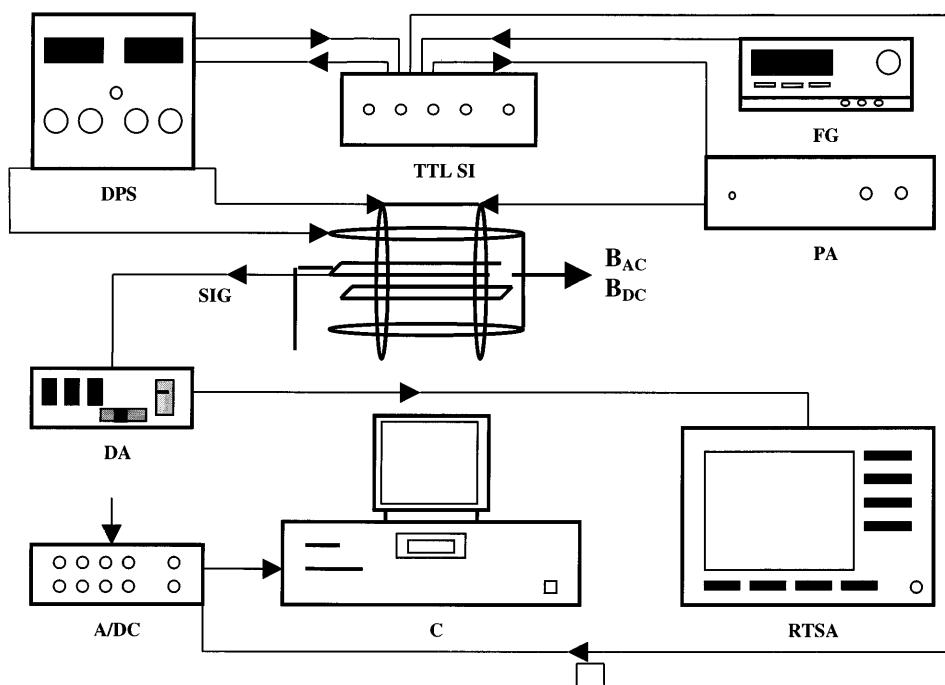


FIG. 2. Schematic representation of instrumentation used to power Helmholtz coils (center) for generating magnetic fields (B_{AC} , B_{DC}), and to acquire signal (SIG) from the animal preparation mounted within the stereotactic instrument (pictured within the Helmholtz coil array). Instruments include: dual power supply (DPS), function generator (FG), power amplifier (PA), differential amplifier (DA), analog-to-digital converter (A/D C), real-time spectrum analyzer (RTSA), computer (C), TTL switch interface (TTL SI).

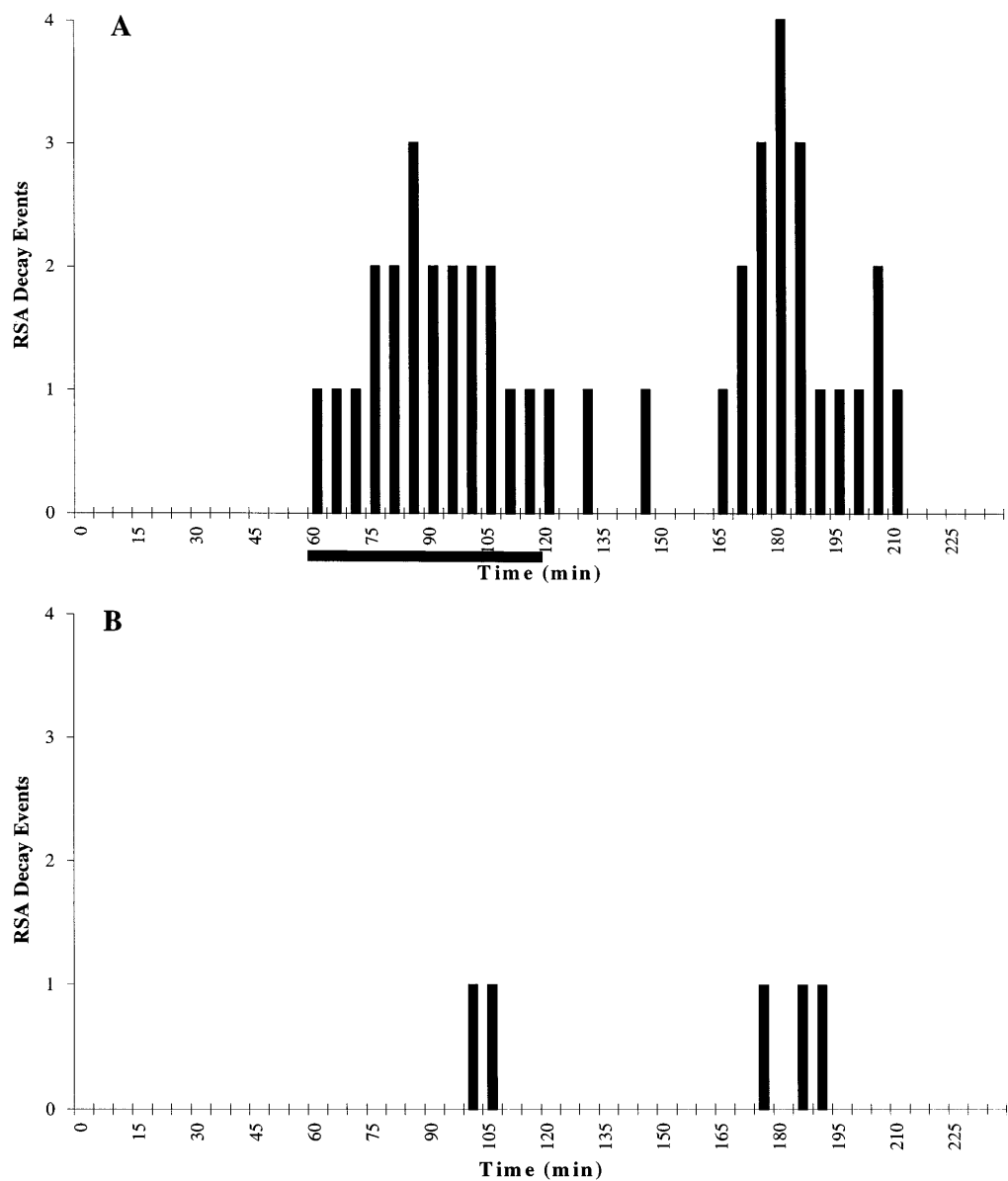


FIG. 3. (A) RSA decay events are plotted as a function of time for the experimental group. AC magnetic field (16.0 Hz; 28.9 μT_{rms}) is applied between 60 and 120 min (indicated by horizontal bar). (B) RSA decay events are plotted as a function of time for the control group, which receives no AC magnetic field exposure.

Pyramidal neurons in the hippocampus possess a large diameter and are organized in parallel arrays which limit extracellular space. This is particularly true in the CA1 stratum pyramidale, where the somas are densely packed within a sharply defined lamina only 50 μm wide. The volume of extracellular space in this region is smaller than in any other neural tissue, resulting in a R_e/R_i ratio of approximately 3 (16). Taylor and Dudek (36) have demonstrated that the movement of positive charge in actively firing pyramidal cells is such that the soma functions as a current sink, whereas neuronal processes, and dendrites in particular, function as current sources, resulting in an electric field

oriented along the pyramidal cell axis. On the basis of these anatomical and physiological considerations they propose that endogenous electric fields resulting from action potential generation within pyramidal neurons produce somatic depolarizations in adjacent pyramidal neurons to the degree that they participate in completing this circuit (36). The AC magnetic fields applied in these experiments were oriented perpendicular to the hippocampal lamella and pyramidal cell axes. Thus, according to Faraday's law, the induced circuitual AC electric fields and their associated currents were parallel to these lamella and were therefore optimally configured to

influence pyramidal cell excitability in the same manner as has been suggested for endogenous field interactions.

Critical to this discussion are the relative magnitudes of endogenously generated and Faraday-induced fields. The field strengths associated with hippocampal RSA, which are putatively involved in endogenous field effects, range between 0.5 and 4 mV/mm, whereas the Faraday-induced field strengths achieved in the present investigation, assuming interactions confined to immediately adjacent pyramidal neurons, are much lower, approximately 10^{-7} mV/mm. Although this disparity is difficult to reconcile, it must be remembered that the field intensities achieved during RSA may be well in excess of the threshold intensity required for endogenous field-mediated synchrony. It is also possible that detection of such weak signals is mediated by mechanisms involving larger spatial domains within the hippocampus. Assuming only linear interactions, this would imply a form of volume conduction within pyramidal networks resulting in an increased cross-sectional area and a proportional increase in induced current. A more plausible hypothesis, however, is suggested by recent findings that neuronal networks, representative of those in the hippocampus, are capable of amplifying weak signals via a stochastic resonance mechanism in a manner requiring only a nonspecific source of noise (above a minimum threshold level), i.e., that associated with the firing patterns of individual neuronal elements (15). Such a mechanism may be utilized routinely to amplify endogenous fields during the initiation and/or propagation of synchrony within the hippocampus. Faraday-induced currents generated by an exogenous alternating magnetic field might therefore be similarly amplified within the CA1 hippocampal network and exert their destabilizing effects on RSA by perturbing these processes.

A particularly intriguing aspect of the data obtained in this investigation is the persistence of RSA instability during the postexposure interval. This persistence implies that hippocampal network dynamics are encoded in some fashion and that they can exert an influence on the future dynamics of the system. Such encoding may involve mechanisms analogous to those which mediate long-term potentiation (13), particularly since hippocampal LTP is optimized when stimuli are delivered at RSA frequencies (23). In the present context this may reflect an adaptation response of the network to the perturbation associated with the magnetic field exposure. This interpretation is suggested both by the decline in the probability of RSA decay events during the last 30 min of the exposure period and by the relatively discrete nature of the RSA decay during the postexposure interval, possibly representing a return of the system to baseline levels following an interval where perturbation was absent.

The possibility that the effects observed in these

investigations were mediated by direct AC magnetic field coupling within the brain, rather than by Faraday-induced currents, must also be considered. The presence of biogenic magnetite in the mammalian brain (22), together with reports that DC magnetic fields are capable of modulating enzyme kinetics (14, 29), are consistent with this possibility. Magnetite is typically found within magnetically polarized aggregates called magnetosomes which, because of their relatively large magnetic moment, represent an optimal site for direct magnetic coupling within cells. Theoretical calculations suggest, however, that for the field intensities employed in these investigations the kinetic energy imparted to these aggregates is still slightly below the threshold required to yield a biological effect (1). Moreover, a role for magnetite in cellular physiology has yet to be established, thus its involvement in regulating enzyme kinetics or neuronal firing characteristics remains entirely speculative.

The magnetic moments associated with other biological constituents are vastly smaller than that of magnetosomes (1). Thus, direct magnetic field interactions involving these constituents would again require some form of amplification in order to become biologically relevant. This may involve a stochastic resonance mechanism analogous to that proposed earlier in connection with Faraday induction, perhaps within networks of membrane-associated proteins. Calmodulin-dependent phosphorylation reactions involving such proteins mediate the expression of LTP (2) and are reportedly affected by magnetic fields in a manner consistent with a direct coupling mechanism (14, 29).

Finally, there is the possibility that RSA destabilization results from current injection into the CNS produced by field interactions involving the electrodes rather than by interactions with tissue. Such current injection could theoretically result from Faraday induction both within individual electrodes (monopolar injection) and between the recording and reference electrodes (bipolar injection). By sacrificing several animals, still mounted for recording, and measuring the signal induced during field application once brain electrical activity had ceased, we determined the magnitude of these currents to be approximately 6 nA for the configuration employed in this investigation. Though Bawin *et al.* (4) has observed that current injection of up to 3.5 μ A failed to disrupt hippocampal RSA *in vitro*, the potential involvement of these currents cannot be entirely ruled out.

Fortunately, the nature of the effects we observed in these investigations are such that carefully designed experiments could distinguish between the competing hypotheses outlined above. For example a Faraday induction mechanism would require that the magnitude of these effects be inversely proportional to the angular displacement of the AC field from the horizon-

tal, becoming zero at $\Theta = 90^\circ$. Also, the persistence of RSA instability during the postexposure interval might permit an indirect determination of whether these effects are mediated by current injection via the electrodes, since this instability could still be detected were the electrodes positioned for recording only after the exposure interval. Clearly further investigation is required to resolve these mechanistic issues. Regardless of their outcome, however, the extreme sensitivity of hippocampal RSA to seemingly minuscule perturbations must be acknowledged.

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